REMARKS

Applicant respectfully requests reconsideration and allowance of the subject application.

Claims 7, and 73 are canceled in this response, their contents moved to their base claims.

Claims 1, 4-5, 8-9, 16, 71, and 74 are amended in this Response.

New claims 75-80 are added in the Response.

Claims 1-2, 4-5, 8-9, 11, 16, 21-23, 71-72, and 74-80 are currently pending examination.

Rejections under 35 U.S.C. §102(b)

The Office rejected claims 1-2, 4-5, 7-9, 11, 16, 21-23, and 71-74 under 35 USC 102(b) as being anticipated by Chenchik et al. (U.S. Patent No. 5,759,822).

The Office also rejected the same claims 1-2, 4-5, 7-9, 11, 16, 21-23, and 71-74 under 35 USC 102(b) as being anticipated by Gordon et al. (U.S. Patent No. 6,607,911).

Claim 1

In light of the Examiner Interview, Applicant amends claim 1 and some of the other pending claims for clarity: "to more particularly point out and distinctly claim the subject matter."

Claim 1 as amended defines a method of creating a clinical reference solution that emulates clinically relevant sites on genes responsible for

human genetic conditions, wherein the clinical reference solution is substantially free of clinically irrelevant nucleic acid, comprising:

- for each clinically relevant site, designing an arrangement of bases to emulate the clinically relevant site as isolated from clinically irrelevant nucleic acid that occurs adjacent to the corresponding clinically relevant site in vivo, wherein the arrangement of bases also forms one or more primer targets for differentially amplifying the clinically relevant site;

- for each clinically relevant site, synthesizing base-by-base, from end to end, a single strand of bases comprising the arrangement of bases that emulates the clinically relevant site and forms the primer targets associated with the clinically relevant site; and

- mixing each single strand into a single solution.

Chenchik and/or Gordon, on the other hand, do not show or disclose each element of Applicant's claim 1.

The Chenchik Reference

The Chenchik reference discloses a method for producing oligonucleotide fragments to modulate amplification through suppression. The method is not, and does not work as, a reference solution. The Chenchik method uses complementing "adapter" regions on a single-stranded oligonucleotide that form loop structures in the absence of complementary fragments that do not amplify by PCR. The Chenchik reference requires interaction with the sample of interest and improves upon current, commonly used, known testing practices. The Chenchik method is used to enhance methods to test for the presence of different mutations and genetic conditions.

Claim 1, in contrast, produces single-stranded oligonucleotide fragments that amplify with a common primer pair. Such oligonucleotides do not contain complementary regions that allow the formation of loop structures. The resulting fragments are used independently of a test specimen. They contain primer regions, but these are for common amplification and may not be complementary or generate a loop structure. These fragments actually comprise the different mutations and genetic variations in a reference solution (rather than test or probe for them).

With regard to particular passages of Chenchik cited as anticipating elements of claim 1:

The Office cites Chenchik column 11, lines 27-28 to show that Chenchik teaches a pure clinical reference solution for testing multiple genetic conditions. However, Chenchik column 11, lines 27-28 refers to optional reagents within a kit

that may be used in conjunction with the Chenchik invention. Chenchik does not teach a method of creating a clinical reference solution for testing multiple genetic conditions any more that it teaches a method for creating an amplification enzyme or PCR primers. These "optional" reagents in Chenchik include polymerases, dNTPs, ligases, enzyme and various buffers and none of these components are described by or specifically covered in the methods for the Chenchik reference. The Chenchik reference describes a method for PCR suppression to achieve selective amplification to improve upon common molecular testing methods already in place in the field.

The Office cites Chenchik column 13, lines 2-8 to show that Chenchik teaches a clinical reference solution to test for conditions such as chromosome aberrations including point mutations, deletions, insertions, transversions and other conditions. However, claim 1 involves determining and designing one or more clinically relevant sites on one or more nucleic acid sequence that may be detected or determined by various methods. The method of claim 1 is not used to "determine" or "map" chromosome aberrations, point mutations, etc., in test samples.

The Office cites Chenchik column 24, lines 8-12 to show a clinical reference solution free of clinically irrelevant nucleic acid. However, regarding column 24, lines 8-12, example 4 refers rather to the application of the finished product (suppression fragments) to produce a cDNA library free from poly A-minus fractions or genomic impurities.

The Office cites Chenchik column 24, lines 15-17 to show an arrangement of bases that also includes one or more primer targets, but in column 24, lines 15-

17, the adaptor used in the Chenchik reference is a region of bases designed to anneal with a complementary region at the opposing end of the Chenchik fragment. The attachment of primer binding regions to single-stranded DNA fragments is not novel. In applicant's claim 1, however, the purpose and role of the primer target in the overall amplification methodology is novel. Every single-stranded oligonucleotide carrying the same primer tags can generate its own complementary fragment and can amplify exponentially with the single primer pair.

The Office cites Chenchik column 24, lines 18-22 to show synthesizing, base-by-base, a single-stranded artificial version of each arrangement of bases associated with each clinically relevant site. However, regarding column 24, lines 18-22, synthesizing base-by-base is different from amplifying regions of interest using a poly-A primer and unique primer. The "unique" primer refers to a naturally occurring base sequence that can be used to selectively amplify the region of interest from the genomic subset. Claim 1, on the other hand, uses base sequences that can and usually are independent of genomic origin.

The Office cites Chenchik column 13, lines 9-29 and column 12 lines 66 to column 13 lines 2 to show mixing each artificial version of a clinically relevant site into a single solution (fragments can be cloned into a plasmid or other vector for use as a reference).

However, Chenchik column 13, lines 9-29, describes a method to equalize uneven populations of cDNA fragments in a cDNA library. After the sample division and adapter ligation, each Chenchik fragment only carries a single primer binding site. It is not until the two mixes are combined that exponential

amplification may occur from complementary annealing of two fragments each only carrying a single primer binding site of the two primers.

Regarding Chenchik column 12 lines 66 to column 13 lines 2, this sentence refers to standard recombinant vectors such as plasmids and YAKs containing cloned DNA regions or "fragments." These fragments that are referred to are not the fragments designed in the Chenchik reference. The Chenchik fragments must remain independent of a vector to function. The single-stranded loop structure would be inhibited and their role as a suppressor would be blocked if they were inserted into a vector. The standard reference clones are mixed with genomic samples in the presence of the Chenchik constructs.

The Gordon Reference

In contrast with Gordon, the methodology defined in Applicant's claims does not require the use of vectors or any double-stranded constructs. Rather, Applicant's technique employs a mix of single-stranded oligonucleotides that are able to be exponentially amplified directly (starting from single-stranded fragments). One single primer pair amplifies every fragment mimicking a clinically relevant site in the control mixture. By varying the concentration of each reference oligonucleotide or primer pair, the amplification of all of the differing control oligonucleotides can be modulated to produce a standardized mix of PCR amplicons for all mutations of interest in a test method. This is beyond the scope of the Gordon patent. The Gordon reference refers to producing double-stranded DNA products and primarily deals with utilizing primers specific to each cassette fragment to generate an appropriate level of PCR amplicon to be used for

cloning methods to generate each cassette. While both methods employ the use of primers and PCR amplification, the design and application of these methods are used in a manner to produce fundamentally different results at completely different stages. The purpose of the Gordon methodology, in reference to introduced PCR primer sites, is to produce a pure (cassette specific) collection of double-stranded fragments for each single cassette that will eventually be used for digestion and subsequent ligation 5' to 3' into a construct containing a vector. The added primer sites introduce restriction sites for subsequent cloning experiments, as is common practice. The constructs carrying one or more of these "cassettes" in a vector comprise a finished control product as explained in the Gordon reference. The artificial primer sites that were introduced for generating "cassettes" are not used in ways beyond those illustrated therein or in the downstream testing or additional amplification of these cassettes by the test methods for which these controls are designed.

The Gordon methodology generates double-stranded fragments that are then ligated into a vector to produce a single control molecule carrying multiple mutations "in series". Applicant's methodology, in contrast, produces small fragments that are single-stranded and amplify exponentially by either an internal or external primer pair based on the design of the artificial tags introduced at the 5' and 3' end of each fragment. Thus, Applicant's control carries multiple control molecules "in parallel" which is not anticipated by Gordon.

Since neither Chenchik nor Gordon show or disclose all the elements of claim 1, the 35 USC 102(b) rejections fail. Applicant respectfully requests that the rejection be removed, and that claim 1 be allowed.

Claim 2

The Office again cites column 13 lines 2-8 to show that Chenchik teaches a method in which each clinically relevant site comprises a mutation of a normal human nucleic acid sequence. However, again, this refers to developing a fragment to test for the condition, not to produce a single-stranded reference fragment that mimics a genomic reference sample.

Since Chenchik and Gordon do not show or disclose each element of Applicant's claim 2, Applicant respectfully requests that the 35 USC 102(b) rejection be removed, and that claim 2 be allowed.

Claim 4

With regard to claim 4, the Examiner cites Chenchik column 14, lines 5-6. This passage is merely a description of standard PCR. The gist of the Chenchik reference involves directly evaluating a test sample and modifying the cDNA or genomic components with two or more sets of primers/adaptors and mixing these samples back together to create complementary structures that will selectively amplify the region of interest. Applicant's claim, on the other hand, is a method of producing a "synthetic test sample" that carries all of the mutations of interest and performs independently from the test sample (e.g., similar to how a calibration solution is not the same as the sample to be tested). Applicant's claims define a

method to produce mutation reference standards that can be used to evaluate the Chenchik or many other PCR-based testing methods. Applicant's single-stranded oligonucleotides do not require a complementary strand carrying an additional primer binding site/adaptor to carry out exponential amplification (Applicant's oligonucleotide is one strand with both primers – one direct and one complementary).

Since Chenchik and Gordon do not show or disclose each element of Applicant's claim 4, Applicant respectfully requests that the 35 USC 102(b) rejection be removed, and that claim 4 be allowed.

Claim 5

With regard to claim 5, the Office cites Chenchik column 11, lines 62-67. However, this passage refers to standard sample types and test products that the Chenchik method can be used on. In contrast, Applicant's ligation procedure is used to ligate multiple of Applicant's synthesized oligonucleotides to create larger native sequences between Applicant's primer tags for the purpose of building a larger fragment for reference testing. Hence, the same primer is not ligated onto multiple constructs.

Since Chenchik and Gordon do not show or disclose each element of Applicant's claim 5, Applicant respectfully requests that the 35 USC 102(b) rejection be removed, and that claim 5 be allowed.

Claims 8-9, 11, 16, 21-23, and new claims 75-77

For at least the reasons describe above with respect to claim 1 and with respect to claims 2-5, the other claims that are dependent on claim 1—i.e., claims 8-9, 11, 16, 21-23, and new claims 75-77—are also allowable. Dependent claims contain the language of their respective base claims. Claims 8-9, 11, 16, 21-23, and new claims 75-77 depend from claim 1. Thus, claims 8-9, 11, 16, 21-23, and new claims 75-77 are also allowable.

Claim 71

Applicant respectfully submits that base claim 71 is allowable for the same reasons given above for claim 1. Claim 71 includes the feature that different groups of synthetically generated oligonucleotides mimicking clinically relevant sites can be differentially amplified in groups.

Claims 72 and 74

For at least the reasons describe above with respect to claim 71, claims 72 and 74 are also allowable. Dependent claims contain the language of their respective base claims. Claims 72 and 74 depend from claim 71. Thus, claims 72 and 74 are also allowable.

New claims 78-80

Claims 78-80 define in less words than the other claims a single-stranded nucleic acid reference fragment that mimics a clinically relevant site of a genomic

reference sample. Conventional genomic reference samples have vast amounts of irrelevant genomic nucleic acid and/or vast amounts of plasmid / cloning material together with a relatively smaller amount of the mutation or clinical site of interest. Applicant's single-stranded nucleic acid reference fragments create a clinical reference solution that is substantially composed of pure mutations or pure clinically relevant sites.

Conclusion

The Applicant submits that all of the remaining claims are in condition for allowance and respectfully requests such allowance. If unresolved issues remain, Applicant respectfully requests that the undersigned attorney be contacted for scheduling an interview.

Respectfully Submitted,

Dated: March 5, 2007 By: /Mark Farrell/

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